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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,575	11/28/2000	Dale B. Schenk	15270-005912	6096
20350	7590	05/06/2005		
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834				
			EXAMINER	
			NICHOLS, CHRISTOPHER J	
			ART UNIT	PAPER NUMBER
			1647	
DATE MAILED: 05/06/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.	Applicant(s)
09/724,575	SCHENK, DALE B.
Christopher J. Nichols, Ph.D.	1647

- The MAILING DATE of this communication appears on the cover sheet with the correspondence address -  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- Responsive to communication(s) filed on 29 July 2004.
- This action is **FINAL**.  This action is non-final.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- Claim(s) 11,58 and 74-81 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- Claim(s) \_\_\_\_\_ is/are allowed.
- Claim(s) 11,58 and 74-81 is/are rejected.
- Claim(s) \_\_\_\_\_ is/are objected to.
- Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- The specification is objected to by the Examiner.
- The drawing(s) filed on 21 May 2003 is/are: a)  accepted or b)  objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All b)  Some \* c)  None of:
  - Certified copies of the priority documents have been received.
  - Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- Notice of References Cited (PTO-892)
- Notice of Draftsperson's Patent Drawing Review (PTO-948)

- Interview Summary (PTO-413)  
Paper No(s)/Mail Date: 9/20/05
- Notice of Informal Patent Application (PTO-152)

**DETAILED ACTION**

***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 July 2004 has been entered.
2. The Petition from Requirement for Restriction filed 30 December 2003 has been GRANTED-IN-PART on 14 October 2004. Pursuant to the Decision on Petition: (1) The Restriction Requirement mailed 23 March 2002 is hereby VACATED, (2) The Finality of the Office Action mailed 25 July 2003 is hereby *withdrawn*, and (3) Prosecution on the merits is hereby *reopened*.

***Status of Application, Amendments, and/or Claims***

3. The Amendment filed 24 January 2005 has been received and entered in full.
4. The Amendment filed 31 January 2005 has been received and entered in full.

***Withdrawn Objections And/Or Rejections***

5. All previous Objections are hereby *withdrawn* in view of Applicant's amendments (29 July 2004, 24 January 2004, and 31 January 2004) and in view of the Decision on Petition (14 October 2004).
6. All previous Rejections are hereby *withdrawn* in view of Applicant's amendments (29 July 2004, 24 January 2004, and 31 January 2004) and in view of the Decision on Petition (14 October 2004).
7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Objections***

8. Claim 11 is objected to because of the following informalities: the claim ends with the phrase "therapeutically treat the disease". This limitation is unclear and does not serve to limit the claim or add functional language to the method. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

9. Claims 11 and 74-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *method of therapeutically treating a patient suffering from Alzheimer's disease, comprising administering to the patient a dosage of an chimeric or humanized antibody or antibody fragment thereof that specifically binds synuclein-NAC and a dosage of an chimeric or humanized antibody or antibody fragment thereof that specifically*

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*binds to an epitope within residues 1-28 of A $\beta$ , and thereby effecting treatment of the disease,* does not reasonably provide enablement for *using non-chimeric, non-humanized, or, non-specific anti-A $\beta$  antibodies*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

10. The claims are drawn very broadly to methods of treating Alzheimer's disease comprising administering two antibodies, one which binds synuclein-NAC and the other which binds A $\beta$ . The language of said claims encompasses any antibody so long as one binds synuclein-NAC and the other which binds A $\beta$ . The antibodies are not required to have any other structural parameters or functional characteristics.

11. The specification teaches that the administration of particular A $\beta_{42}$  (AN1792) fragments with an immunogenic adjuvant reduces  $\beta$ -amyloid levels within the brains of transgenic PDAPP mice (Figures 7-9 and 11-12). These mice exhibit Alzheimer type over production and build up of A $\beta$  within the brain. The Specification teaches that both *active* (immunogenic peptide) and *passive* (antibodies) immunization is applicable to relieve symptoms of Alzheimer's disease in PDAPP mouse model (pp. 6-8).

12. The Specification demonstrates an actual reduction to practice of *active immunization* by administration of an AN1792 which decreases cortical amyloid plaque burden and neuritic plaque burden (Figures 7-8). The Specification also teaches an actual reduction of practice of *passive immunization* via administration of three antibodies against A $\beta$  (polyclonal, 10D5, and 2F12) all of which show a decline in the amyloid and A $\beta$  burden in the PDAPP mouse model *versus* a PBS control (Tables 13-15). The Specification also includes prophetic guidance for use

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of synuclein-NAC, with and without A $\beta$ , for *passive immunization* (pp. 19, 60; Examples V, VI, XI, and XII).

13. In the art, Brookes & St Clair (October 1994) "Synuclein proteins and Alzheimer's disease." Trends Neurosci. 17(10): 404-5 teaches that in Alzheimer's disease, synuclein-NAC (non-A $\beta$  component of Alzheimer's disease amyloid) proteins are found in presynaptic cholinergic nerve terminals that degenerate early in Alzheimer's disease. Synuclein-NAC is also found closely linked to A $\beta$  fibrils in senile plaques.

14. However, the specification fails to provide any guidance for the successful treatment of Alzheimer's disease using an immunogenic agent other than AN1792 which is a N-terminal fragment, known to be immunogenic. And since resolution of the various complications in regards to targeting the role a particular epitope to generate a useful antibodies or a desirable immune response is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with antibodies to correlate with relief of Alzheimer's disease. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

15. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an antibody therapy based solely on its performance of a *single example* as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and

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discloses general methodologies of using the claimed methods in *in vivo* therapies, such a disclosure would not be considered enabling since the state of *passive immunization* Alzheimer's disease therapy is highly unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

16. The following references are cited herein to illustrate the state of the art of *passive immunization* and Alzheimer's disease.

17. On the state of the prior art, Clayton & George (June 1998) "The synucleins: a family of proteins involved in synaptic function, plasticity, neurodegeneration and disease." Trends Neurosci. 21(6): 249-54 teaches that synuclein fragments have been specifically implicated in three diseases: Alzheimer's (AD) Parkinson's (PD) and breast cancer (pp. 253). In AD, a peptide derived from  $\alpha$ -synuclein forms an intrinsic component of plaque amyloid. Thus it is plausible to use anti-synuclein-NAC antibodies in conjugation with anti- $\text{A}\beta$  for purposes of passive immunization.

18. However, on the breadth of the claims, Solomon (December 2002) "Immunological approaches as therapy for Alzheimer's disease." Expert Opin Biol Ther. 2(8): 907-917 teaches

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that only antibodies targeting the N-terminus of A $\beta$  (residues 1-28) have any anti-aggregating properties (including solubilization of existing aggregates and inhibition of aggregation) (pp. 909). Thus rendering other anti-A $\beta$  antibodies of no use to practice the instant invention. This is further substantiated by the failure of antibodies 16C11 and 12F12 (both directed against the C-terminus of A $\beta$ ) to stimulate phagocytosis of A $\beta$  plaques in an *ex vivo* assay in contrast to N-terminal specific antibodies, 10D5 and 3D6 (pp. 114 Example XIV). While it is noted that an invention may have non-enabled embodiments, Solomon and the Specification specifically teaches that only antibodies against the first 28 residues (N-terminus) are operable [MPEP §2164.08(b)].

19. On the level of predictability in the art, in view of the ELAN News (1/18/02 and 3/1/02) (IDS), murine proteins are especially immunogenic in humans.

20. On the nature of the invention, Goldsby *et al.* (2002) Kuby Immunology 4<sup>th</sup> Ed. Chapter 18 "Vaccines" (pp. 449-465) teaches that passive immunization does not allow for the formation of immunological memory requiring continued dosages if the desired immunity is to be maintained. Also the issue of the antigenicity of the antibody administered must be taken into consideration because it can trigger and unwanted and possibly harmful immune response especially mouse antibodies administered to humans (pp. 451). Therefore inadequate guidance is presented in the Specification to overcome these obstacles in practicing the invention to the full scope as claimed.

21. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from N-terminal antibodies to the full scope of claims as exemplified in the references herein.

22. Claims 58 and 78-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *method of prophylactically treating a patient suffering from Alzheimer's disease, comprising administering to the patient a dosage of an chimeric or humanized antibody or antibody fragment thereof that specifically binds synuclein-NAC and a dosage of an chimeric or humanized antibody or antibody fragment thereof that specifically binds to an epitope within residues 1-16 of A $\beta$ , and thereby effecting prophylaxis of the disease*, does not reasonably provide enablement for *using non-chimeric, non-humanized antibodies, or non-N-terminal specific anti-A $\beta$  antibodies*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make or use** the invention commensurate in scope with these claims.

23. The claims are drawn very broadly to methods of prophylaxis for Alzheimer's disease comprising administering two antibodies, one which binds synuclein-NAC and the other which binds A $\beta$ . The language of said claims encompasses any antibody so long as one binds synuclein-NAC and the other which binds A $\beta$ . The antibodies are not required to have any other structural parameters or functional characteristics.

24. The specification teaches that the administration of particular A $\beta$ <sub>42</sub> (AN1792) fragments with an immunogenic adjuvant reduces  $\beta$ -amyloid levels within the brains of transgenic PDAPP mice (Figures 7-9 and 11-12). These mice exhibit Alzheimer type over production and build up of  $\beta$ -amyloid within the brain. The Specification teaches that both *active* (immunogenic peptide) and *passive* (antibodies) immunization is applicable to relieve symptoms of Alzheimer's disease in PDAPP mouse model (pp. 6-8).

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25. The Specification demonstrates an actual reduction to practice of *active immunization* by administration of an AN1792 which decreases cortical amyloid plaque burden and neuritic plaque burden (Figures 7-8). The Specification also teaches an actual reduction of practice of *passive immunization* via administration of three antibodies against A $\beta$  (polyclonal, 10D5, and 2F12) all of which show a decline in the amyloid and A $\beta$  burden in the PDAPP mouse model versus a PBS control (Tables 13-15). The Specification also includes prophetic guidance for use of synuclein-NAC, with and without A $\beta$ , for *passive immunization* (pp. 19, 60; Examples V, VI, XI, and XII).

26. In the art, Brookes & St Clair (October 1994) "Synuclein proteins and Alzheimer's disease." Trends Neurosci. 17(10): 404-5 teaches that in Alzheimer's disease, synuclein-NAC (non-A $\beta$  component of Alzheimer's disease amyloid) proteins are found in presynaptic cholinergic nerve terminals that degenerate early in Alzheimer's disease. Synuclein-NAC is also found closely linked to A $\beta$  fibrils in senile plaques.

27. However, the specification fails to provide any guidance for the successful prophylaxis of Alzheimer's disease using an immunogenic agent other than AN1792 which is a N-terminal fragment, known to be immunogenic. And since resolution of the various complications in regards to targeting the role a particular epitope to generate a useful antibodies or a desirable immune response is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state-of-the-art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with antibodies to correlate with prophylaxis of

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Alzheimer's disease. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

28. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an antibody therapy based solely on its performance of a *single example* as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapies, such a disclosure would not be considered enabling since the state of *passive immunization* Alzheimer's disease therapy is highly unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

29. The following references are cited herein to illustrate the state of the art of *passive immunization* and Alzheimer's disease.

30. On the state of the prior art, Clayton & George (June 1998) "The synucleins: a family of proteins involved in synaptic function, plasticity, neurodegeneration and disease." Trends Neurosci. 21(6): 249-54 teaches that synuclein fragments have been specifically implicated in the diseases: Alzheimer's (AD) Parkinson's (PD) and breast cancer (pp. 253). In AD, a peptide

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derived from  $\alpha$ -synuclein forms an intrinsic component of plaque amyloid. Thus it is plausible to use anti-synuclein-NAC antibodies in conjugation with anti-A $\beta$  for purposes of passive immunization.

31. However, on the breadth of the claims, Solomon (December 2002) "Immunological approaches as therapy for Alzheimer's disease." Expert Opin Biol Ther. 2(8): 907-917 teaches that only antibodies targeting the N-terminus of A $\beta$  (residues 1-28) have any anti-aggregating properties (including solubilization of existing aggregates and inhibition of aggregation) (pp. 909). Thus rendering other anti-A $\beta$  antibodies of no use to practice the instant invention. This is further substantiated by the failure of antibodies 16C11 and 12F12 (both directed against the C-terminus of A $\beta$ ) to stimulate phagocytosis of A $\beta$  plaques in an *ex vivo* assay in contrast to N-terminal specific antibodies, 10D5 and 3D6 (pp. 114 Example XIV). While it is noted that an invention may have non-enabled embodiments, Solomon and the Specification specifically teaches that only antibodies against the first 28 residues (N-terminus) are operable [MPEP §2164.08(b)].

32. On the level of predictability in the art, in view of the ELAN News (1/18/02 and 3/1/02) (IDS), murine proteins are especially immunogenic in humans.

33. On the nature of the invention, Goldsby *et al.* (2002) Kuby Immunology 4<sup>th</sup> Ed. Chapter 18 "Vaccines" (pp. 449-465) teaches that passive immunization does not allow for the formation of immunological memory requiring continued dosages if the desired immunity is to be maintained. Also the issue of the antigenicity of the antibody administered must be taken into consideration because it can trigger and unwanted and possibly harmful immune response especially mouse antibodies administered to humans (pp. 451). Therefore inadequate guidance is

presented in the Specification to overcome these obstacles in practicing the invention to the full scope as claimed.

34. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from N-terminal antibodies to the full scope of claims as exemplified in the references herein.

35. Claims 11 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

36. The claims requires a antibody which binds to synuclein-NAC while the claims do not specific an epitope nor do the claims require that the antibody's target possess any particular conserved structure, or other distinguishing feature, such as a sequence. Thus, the claims are drawn to a genus of antibodies that is defined by binding anywhere, anyhow to synuclein-NAC. Further, the claims requires a antibody which binds to A $\beta$  while the claims do not specific an epitope nor do the claims require that the antibody's target possess any particular conserved structure, or other distinguishing feature, such as a sequence. Thus, the claims are drawn to a genus of antibodies that is defined by binding anywhere, anyhow to A $\beta$ .

37. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, or any

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combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of a desired target specificity for the antibody in question. The specification does not identify any particular portion of the target (synuclein-NAC and A $\beta$ ) that must be conserved, nor does it provide an epitope. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

38. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) (“the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed”). Thus, an applicant complies with the written-description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” *Lockwood*, 107 F.3d at 1572.

39. In *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 20 January 2004) the CAFC held that “Therefore, based on our past precedent, as long as an applicant has disclosed a “fully characterized antigen,” either by its structure, formula,

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chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

40. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen."

41. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

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*Summary*

42. No claims are allowed.

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*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is (571) 272-0889. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CJN

April 19, 2005

